REMARKS

Claims 1 – 12 and 18 are pending in the application. Claims 5, 6, 10 and 13-17 have been cancelled. Claim 1 has been amended. No new claims have been added. No new matter has been added.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

The Examiner has entered the amendments submitted in the response filed April 29, 2009. The Examiner has withdrawn the rejection to claim 18 under 35 USC §112, first paragraph.

Claim Rejections 35 USC §103(a)

The Examiner has maintained the rejection to claims 1 – 9, 11, 12 and 18 as being unpatentable over the combination of LaCasse et al.(Blood vol. 88 p.1561 (1995)) in view of Marcato et al. (Infection and Immunity vol. 70 p.1279 (3.2002) and Strockbine et al. (J Bacteriology vol. 170 p.1116), Accession Number 2002:397002, Green (US 2002/0081307) and Applicant's admission on page 6, lines 1 – 2 of the specification. Applicants respectfully disagree.

The claims recite a method of reducing, or inhibiting invasiveness and metastasis of tumor cells in a subject, wherein the tumor cells produce Gb3, comprising administering to the subject a therapeutically effective amount of a B-subunit of Shiga toxin, wherein the B-subunit of Shiga toxin is Stx1B or Stx2B.

Again, Applicants point out that Applicants **specifically recite Stx1B or Stx2B** for use in the methods as claimed. Applicants teach that there are a number of Shiga toxin variants and subunits, for example at page 6, beginning at line 30 of the present disclosure:

> The sequences of numerous Shiga toxin variants and subunits are known in the art. For example, the Shiga toxin 1 B-subunit from the E. coli O157:H7 strain is set forth in GenBank Accession Nos. 32400300 and 32400303, the Shiga toxin 2 B-subunit from the E. coli O157:H7 strain is set forth in GenBank Accession No. 13359150, the Shiga toxin 1 A-subunit is set from the E. coli O157:H7 strain is set forth in GenBank Accession Nos. 32400299 and 32400302, and the Shiga toxin 2 A-subunit from the E. coli O157:H7 strain is set forth in GenBank Accession No.15718405.

Further, Applicants have shown that the selected subunit Stx1B selectively kills Gb3 positive cells only. Applicants refer the Examiner to Example 8, on paged 43 - 44 of the present disclosure, where the data shows that **Stx1B selectively causes apoptotic death in cells expressing Gb3**.

The LaCasse reference does not teach or suggest all the limitations of the instant claims. In particular, the LaCasse reference does not teach or suggest a method of reducing, or inhibiting invasiveness and metastasis of tumor cells in a subject, wherein the tumor cells produce Gb3, comprising administering to the subject a therapeutically effective amount of a B-subunit of Shiga toxin, **wherein the B-subunit of Shiga toxin is Stx1B or Stx2B**.

The LaCasse reference is directed to the use of **shiga like toxin (SLT-1) in human bone marrow (BM) purging**. LaCasse uses Shiga Like Toxin (SLT-1) which kills cells by inhibiting protein synthesis. (p.1561). The purpose of the study described by LaCasse "was to establish the potential of a natural toxin (SLT-1) in purging B-cell lymphomas from BM." (p.1563).

LaCasse does not teach or suggest a method of reducing, or inhibiting invasiveness and metastasis of tumor cells in a subject using Stx1B or Stx2B. The Examiner argues that LaCasse teaches administration of SLT-1 and a corresponding increase in disease free survival.

None of the Marcato, Strockbine or Greene references cure the defects of the LaCasse reference. None of the references, alone or in combination, teach or suggest a method of reducing, or inhibiting invasiveness and metastasis of tumor cells in a

subject, wherein the tumor cells produce Gb3, comprising administering to the subject a therapeutically effective amount of a B-subunit of Shiga toxin.

Nowhere in the Marcato reference is there teaching or suggestion of a method of reducing, or inhibiting invasiveness and metastasis of tumor cells in a subject, wherein the tumor cells produce Gb3, comprising administering to the subject a therapeutically effective amount of a B-subunit of Shiga toxin as claimed.

The Examiner argues that Applicant has argued each reference separately. The Examiner argues that "Marcato was cited to show why one skilled in the art would cho(o)se the subunit."' (Office Action, p.4 – 5).

The Examiner argues that "it would have been obvious that one skilled in the art can use the B subunit from either toxin and expect the same results and thus it would have been obvious to one of ordinary skill in the art to use the B subunit of either toxin in the treatment of the primary reference with the expected benefit of treating B cell lymphoma." (Office Action of 5/23/2008, p.8).

The Marcato reference is directed to use of the cloned shiga toxin B (Stx2 B) subunit to induce apoptosis in Burkitt Lymphoma B-cells. Nowhere does Marcato teach inhibiting invasiveness and metastasis of tumor cells in a subject. Further, the Marcato reference teaches that "unlike the two holotoxins, Stx2 B subunit mediated apoptosis does not involve inhibition of protein biosynthesis." (Abstract, p.1279). This is different from the teachings of Lacasse, where SLT-1 kills cells by inhibiting protein synthesis.

One of skill in the art would not be motivated to use StxB, taught by Marcato, in place of SLT-1, taught by LaCasse.

Therefore, the teachings of the cited art, when combined, do not result in the claimed invention.

Accordingly, Applicants request that the rejection be withdrawn and the claims allowed.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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